Aesthetic Medicine 2023; Vol. 9, N. 2: e2023011 DOI: 10.57662/am.v9i2.14994

Original article

Smart PDOs: a system for controlled release in facial aesthetic

Víctor García-Guevara[1], Dubraska Violeta Suárez-Vega[2], Gladys Josefina Velazco de Maldonado[3], Reynaldo Ortiz-Ruiz[4], Blanca Miller-Kobisher[5]

[1]Foundation Center for Aesthetic Medicine Studies (FUCEME); [2]University of Los Andes (ULA), Mérida-Venezuela, Faculty of Dentistry, Department of Investigation, Dental Research Center; [3]University of Los Andes (ULA), Mérida-Venezuela, Faculty of Dentistry, Restorative Dentistry Department, Dental Research Center; [4]University of Los Andes (ULA), Mérida-Venezuela, Science Faculty, Chemistry Department, Electrochemistry Laboratory; [5]Pan-American Institute of Scientific Professionals (IPPC) México City, México

Abstract. We propose a new facial lifting protocol using polydioxanone threads embedded in acetyl hexapeptide-8 (Argireline®). We assume that Argireline® (Arg) reinforces the effects of PDO threads, as it is a mimetic of botulinum toxin. Because the PDO suture is hydrolyzable, this assumption was evaluated through an instrumental analysis. *Objective:* To demonstrate the capacity of the PDO suture as a system for the controlled release of acetyl hexapeptide-8. *Materials and methods:* Three segments of 1cm-long 21G PDO threads were immersed in 1 ml of Arg. PDO threads were observed under an optical, electron microscope at 24, 48, and 72 hours later. They were also weighed before and after being soaked in Arg. Finally, employing UV-Vis spectroscopy, the release rate of Arg from the PDO suture was measured. *Results:* The electronic weighing revealed that the PDO thread enjoys capillarity by the peptide doubling its weight every 24 hours. UV spectra revealed that the PDO thread is a well-controlled release system for Arg, allowing its sustained release for 1 hour. Optical and electronic photomicrographs confirm that the swelling of the PDO thread by absorbing Arg from its capillarity, but this hydrophilicity does not lead to its premature physical degradation. *Conclusions:* The PDO thread system with Arg is an intelligent bioactive system useful in facial harmonization. It is recommended for clinical uses to verify its superior lifting effect.

Key words: Facial absorbable suspension sutures, polydioxanone, acetyl hexapeptide, argireline®, polydioxanone threads

Introduction

It is well known that polymer-based controlled release systems (SLC) are ideal candidates for the sustained release of drugs into the body. Therefore, to modulate the release time, and control drugs delivery kinetics, several approaches have been adopted[1]. Among these, there is currently the use of fibrous matrices and polymeric sutures, which seem to offer important advantages due to their compatibility with a wide variety of drugs[2].

These matrices include polydioxanone (PDO), a polymer that has been used in a variety of biomedical devices, scaffolds, and suture materials, due to its excellent biocompatibility, being the PDO threads are highly flexible, stress-resistant, biodegradable sutures[3].

The usefulness of polydioxanone threads as drug-releasing devices has been analyzed since 2016[4]. It is presumed that its effectiveness as a delivery system is because the drug molecules manage to trap between the fibers of the thread since the fibers have an extremely high absorption surface area, which contributes to a subsequent slow and sustained release of the drug[5].

This phenomenon of drug release from PDO sutures is possible, thanks to the ability of the polymer to absorb water; this property is known as capillarity, which is the ability to absorb fluids along the filament, from the submerged part of the filament to the dry part. Capillarity differs from the ability to absorb fluid, in that fluid absorption is determined when the suture is fully immersed in it[6].

Hence, PDO sutures can absorb drugs and substances of a liquid nature, without necessarily starting their immediate biodegradation through hydrolysis, because although they have capillarity, their biodegradation in the organic environment is slow, up to 180 days to 210 days[7].

For this reason, PDO threads are an option for facial deflation; a successful therapy indicated to reverse deflation, lipomatosis, rhytids, and deep folds when the degree of aging does not require surgical treatments[3].

Having stated all this, you can assume that the physical property of capillarity in Facial Harmonization could become an ally, for the use of the PDO suture as an osmotically controlled release system, being able to impregnate with active principles and slowly release them to the environment. Also becoming a bioactive scaffold, without its wetting irremediably leading to its degradation and immediate loss of important physical properties such as resistance modulus.

Such assertions were tested in the present investigation. The objective was to demonstrate, the ability of PDO suture as a system for the controlled release of acetyl hexapeptide-8 (Argireline®), a biomimetic peptide of botulinum toxin. A delivery system that proposed for a subdermal use in frontal and ocular contour neuromodulation, since the topical penetration of acetyl hexapeptide-8 (Arg) is deficient and a subdermal delivery system would overcome this limitation.

For this, we started from the instrumental analysis of the PDO suture impregnated with the active, evaluating under four types of techniques to check the absorption and release of fluids: a fluid absorption test by electronic weighing, observation by optical microscopy, and scanning electron microscopy. In addition, an analysis of the release rate by UV-Vis spectroscopy was performed.

Materials and methods

The present descriptive research, with a laboratory design or created environment, longitudinal or contemporary evolution[8], considered three specimens as study samples: one for the control-control group (PDO without Arg), one for the control group (embedded PDO in distilled water), and one for the experimental group (PDO loaded with Arg).

The instrumental analysis of the PDO suture impregnated with the peptide was carried out, completing an evaluation evaluating under four types of techniques to verify the absorption and release of fluids: a fluid absorption test by electronic weighing, observation by optical reflection microscopy, and observation by electron microscopy. Furthermore there was a Scanning and analysis of the release rate by UV-Vis spectroscopy.

Materials

- Acetyl hexapeptide-8 peptide in solution, Argireline® brand (Lipotec SAU, Barcelona Spain) 6% w / v 10 ml vial
- Polydioxanone monofilament, nonbarbed, JBP V-Lift Premium® brand (JBP KOREA CO., LTD.), with a diameter 23G gauge (4-0) length 150mm
- Ultrapure water 18 MΩ • cm
- 1ml BD Luer Slip™ hypodermic syringes (BD plastipack® New Jersey-United States) with an interchangeable needle to remove peptide
- 3ml Eppendorf™ DNA LoBind Polypropylene Microcentrifuge Tubes (Hamburg-Germany)

Fluid absorption test by differential weighing

The suture was sterilized and vacuum-packed without any degree of humidity. The thread was extracted from its guide cannula on a sterile field and measurements were made with a millimeter metal ruler to cut three segments of 1 cm in length with sterile surgical scissors.

On an electronic balance (Sartorius CPA analytical); the weight of a 1 cm long segment of the PDO suture without impregnation was determined to set the initial reference value. Subsequently, a segment of the PDO thread immersed in 1 ml of Arg at 6% (w / v) in sterile tubes of 1.5 ml polypropylene microcentrifuge (Eppendorf Safe-Lock®) was labeled for the identification of the samples in three groups. According to the dive time (1 minute, 24, 48, and 72 hours). Once the tubes were covered, they were stored at a temperature of 37 ° C.

Once the immersion time had elapsed, each segment of the thread was removed from the medium of the tube with a sterile clamp and it weighed on the scale. Likewise, a PDO suture segment of the same size was immersed for the same time in 1ml of distilled water, and the respective weight was recorded.

Observation under the light microscope

At the end of each evaluation (24, 48, and 72 hours after immersion), the PDO suture segments were removed from the tube with sterile forceps, dried on a sterile field at room temperature for 5 minutes, mounted on a slide, and observed through the Nikon® reflection optical microscope, at 4x and 10x; a microphotographic scan of each segment was performed.

Scanning electron microscopy

Once the PDO suture had been soaked with Arg for 1 minute, it was removed from the medium with the active ingredient and allowed to dry at room temperature for 5 minutes on the slide. The thread segment was then impregnated on the sheet with a fixative for the electron microscopy samples, or a 3:3 mixture (3% formaldehyde + 3% glutaraldehyde in 0.1M cacodylate buffer, pH 6.3).

The coverslip sheet was previously identified with a lateral cut for its spatial location at the time of metallization and its subsequent mounting in the electron microscope. Both control and experimental slides were stored in capped test tubes immersed in a fixative mixture, refrigerated at 4 ° C, for a minimum of 24 hours for immediate fixation.

After fixation, the samples were dehydrated with ethyl alcohol in increasing concentrations. Desiccation was carried out for 48 hours and they were metalized by being sprayed with gold. They were then observed in a Hitachi S-2500 scanning electron microscope.

Arg release rate from PDO

The PDO-Arg thread was observed indirectly, assisted through a software connected to a UV-Vis spectrophotometer. The program outputs data in the form of codes, corresponding to each absorbance signal in nanometers or the wavelength peaks in the UV spec-

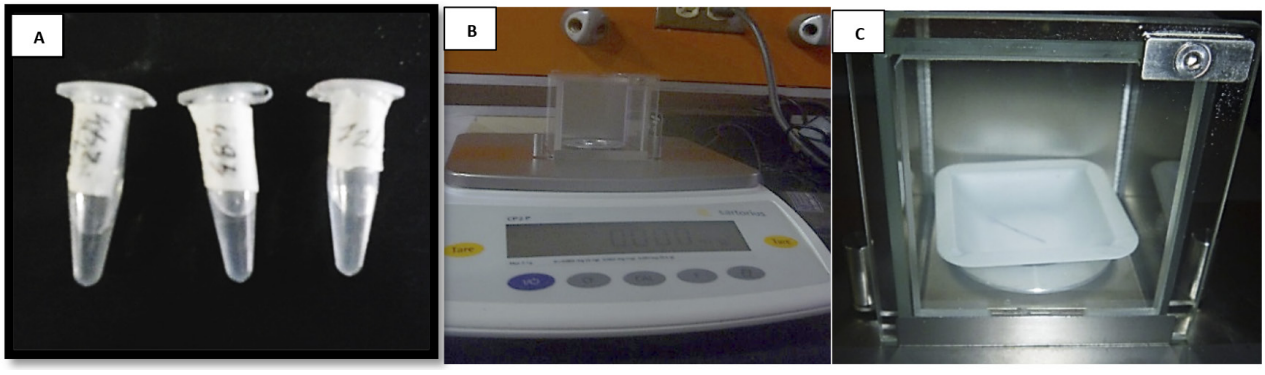


Figure 1. A. PDO segments in the middle of immersion. B. Calibrated electronic balance. C. Purple segment of the PDO Thread in the closed chamber of the electronic balance.

Table 1. PDO thread weight before and after absorbing fluids.

	24 HOURS	48 HOURS	72 HOURS
PDO single	**0.4965 mg**	0.4965 mg	0.4965 mg
PDO + Distilled Water	**0.993 mg**	**0.955mg**	**0.942mg**
PDO + Acetyl Hexapeptide	**1.09mg**	**1,119mg**	**1.95mg**

trum. These signals correspond to the uptake of the drug in water as the photons pass through the cell and the submerged thread. Results were plotted using the Origin Lab® software. The prolonged release of the drug was assessed by recording the release rate of the Arg from the PDO suture and a concentration curve released over time (at 5, 15, 30, 60, and 2400 minutes or 24 hours) was constructed.

Results

Fluid absorption test by differential weighing

The weight of the PDO thread doubles after 24 hours when immersed in distilled water and acetyl hexapeptide-8, exceeding the weight of the thread with water by 10 mg. This weight increased 48 and 72 hours later, both for the control group of the thread soaked in water and for the segment of thread soaked in the peptide, the weight recorded in the PDO thread segment loaded with acetyl hexapeptide being always greater, which suggests a higher molecular weight of the fluid.

Optical microscopy

The photomicrographs at 24 hours already show structural changes in the fibers of the PDO thread with an increase in interlaminar spaces, which are more easily visible in the central column of the thread.

Traces of the violet pigment are also observed moving towards the periphery of the thread (purple line), above a central background of interlaminar and interfibrillar spaces. Both the increased gaps and the pigment outlet correspond to the fluid absorption (Arg) in the fiber.

Optical photomicrograph of the thread at 4X. It is observed in the central column of the thread enlarged at interlaminar and interfibrillar spaces (vertical and parallel whitish bands) corresponding to the penetration of the peptide between the amorphous phase of the polymer, being surface areas where the Drug molecules are trapped between the fibers of the thread.

At 48 hours, figure 3 shows how the PDO thread is capable of absorbing fluids. The hygroscopy of the PDO suture was evident. Being observed as a swelling in the periphery of the thread (retention of an aqueous content between the peripheral layers and the central core of the thread) accompanied by an increase of the interlaminar spaces (whitish stripes), indicative of the hygroscopic phenomenon experienced by the fiber in the presence of the Arg peptide.

a. 4X optical photomicrograph. Note in the central area of the thread a bright light purple column corresponding to the central fiber of the PDO thread surrounded by parallel areas in dark light that extend from the central area to the periphery of the thread (increase in interlaminar spaces).
b. and c. Thread at 10x. Note the increase in interfibrillar spaces and not only interlaminar spaces, they are observed as bright whitish vertical and parallel bands corresponding to the phenomenon of fluid absorption.

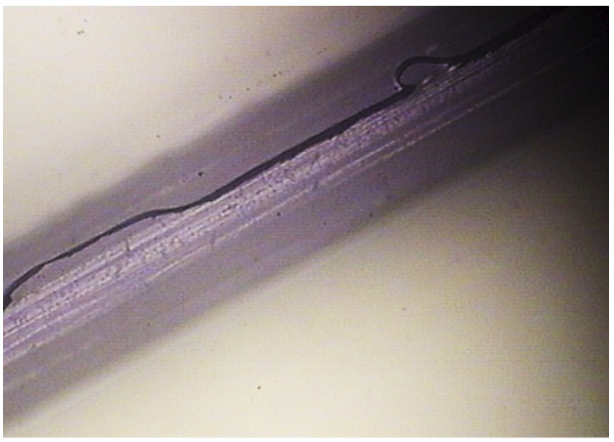


Figure 2. PDO thread after 24 hours immersion in Arg.

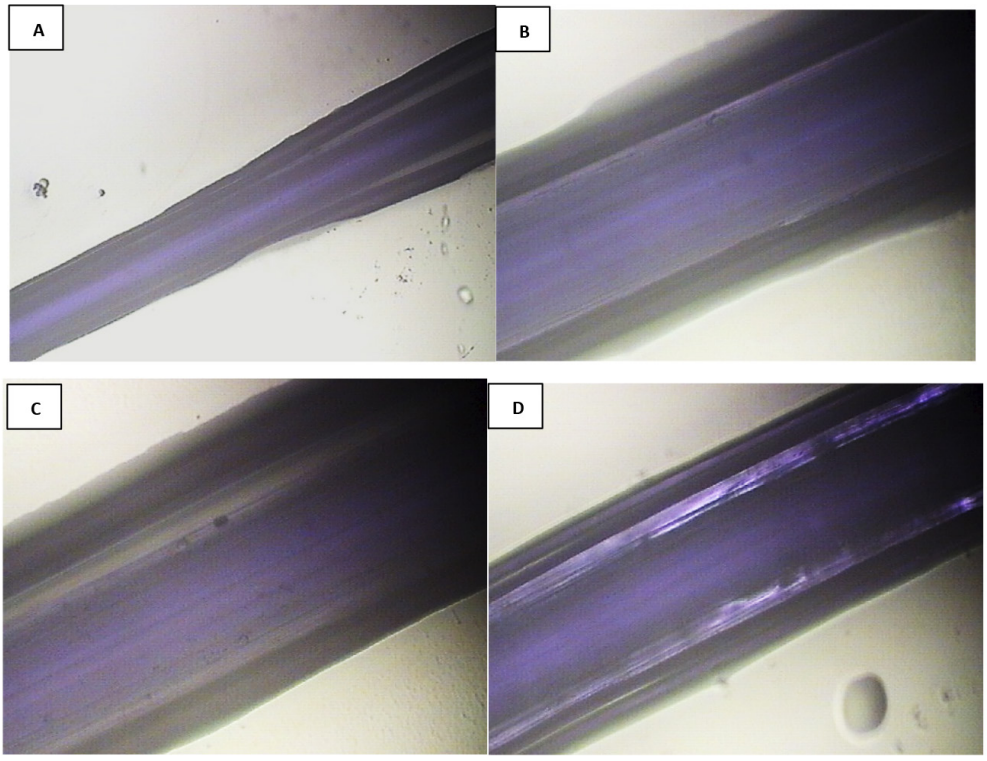


Figure 3. PDO thread after 48 hours of immersion in Arg.

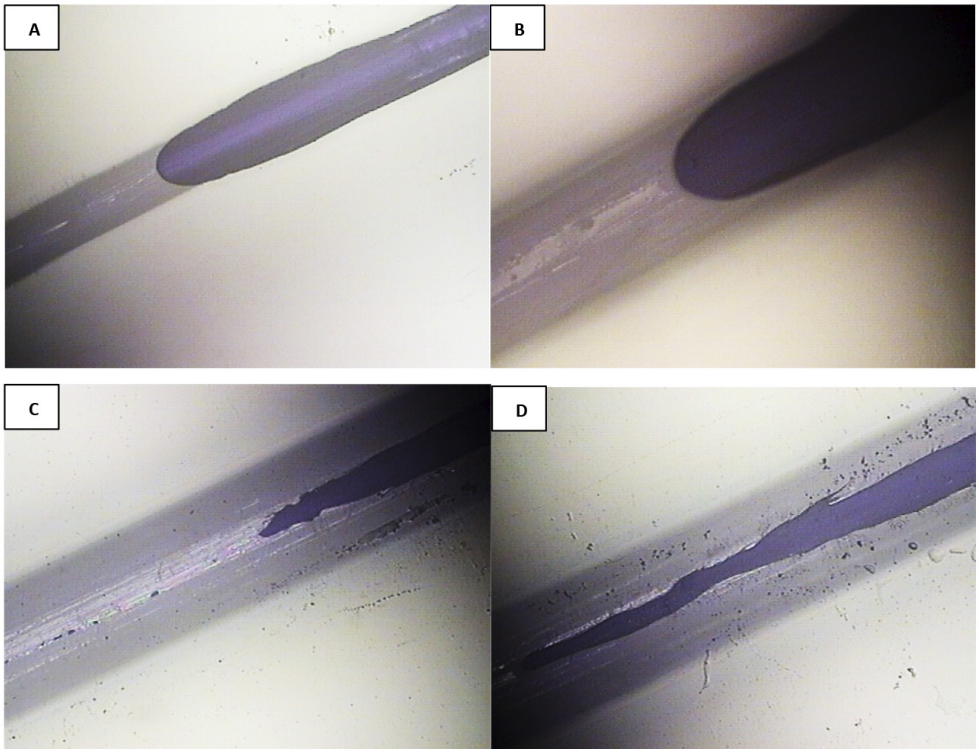


Figure 4. Capillarity of the PDO thread after 48 hours of immersion in Arg.

d. Aqueous retention in the thread was observed at 4x.

Likewise, it was possible to capture the progress of the capillary phenomenon of the PDO suture before its immersion in acetyl hexapeptide. It corresponds to the advancement of a dark purple-pigmented area that interpenetrates the thread (Figure 4).

A and b

Optical photomicrographs of reflection of the thread at 10x and 4x in which the phenomenon of Capillarity is denoted by the effect of fluid absorption along the filament from the embedded part to the dry area of the thread, without completely submerging the thread in the aqueous medium of the active ingredient.

C and d

PDO thread after 72 hours of immersion in Arg at 10x. Note the increase in the thickness of the thread, and the interpenetration of the fluid in the central column of the suture, as well as the migration of the amorphous zone to the crystalline zone of the polymer in the suture.

Scanning electron microscopy

The topography of the smooth PDO threads is seen as homogeneous cylinders with superficial lateral cuts in the form of micro-spicules in opposite directions, which is possibly part of the factory design for their micro anchorage in the subcutaneous tissue (Figure 5a).

When adding the peptide formulation, it was observed that this biomimetic active covers the thread, interpenetrates the fissure of the fiber and in certain sections, it flakes due to the effect of metallization. However, the image shows the indemnity of the PDO thread as when the Arg is added to it, the peptide does not seem to alter the structure of the thread, nor does it hydrolyze it, therefore indicating that the PDO + Arg thread is a physically stable system (Figure 5 b).

Arg release rate from PDO suture

Initially it was required to measure the signal provided independently by the acetyl hexapeptide drug and by the PDO thread in the distilled water where these signals are used to detect how differently they absorbe each drug released in the UV cell.

In graph 1 the spectrum of the PDO suture alone is observed, whose absorbance region is recorded between the 225nm approximately.

Graph 2 shows that the suture emits a maximum absorbance peak of 0.17686 at 30 minutes, stabilizing again after 1 hour, remaining similar until 24 hours. This sweep of spectra of the thread suggests that the

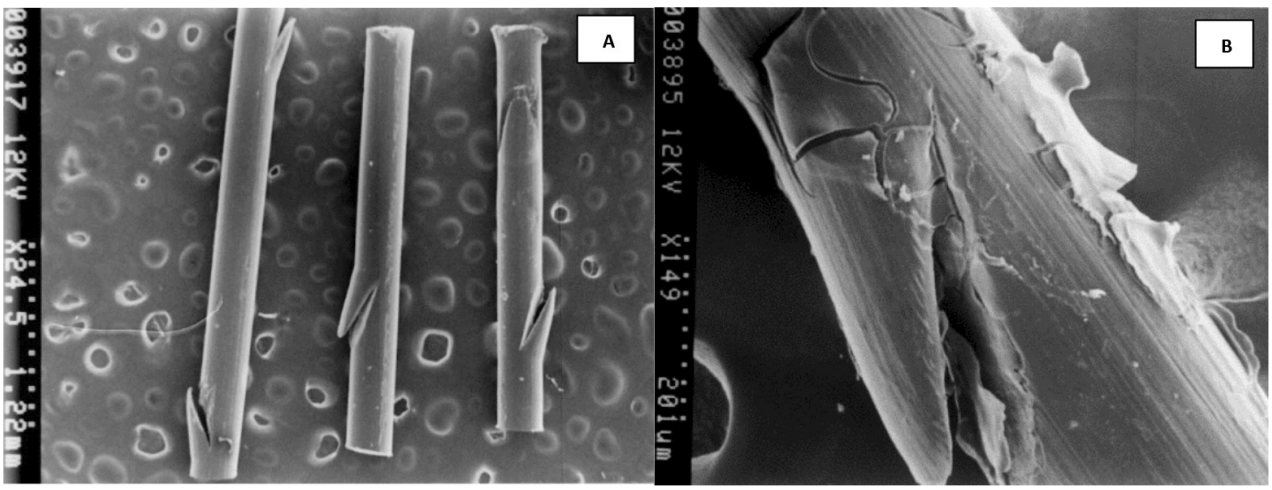
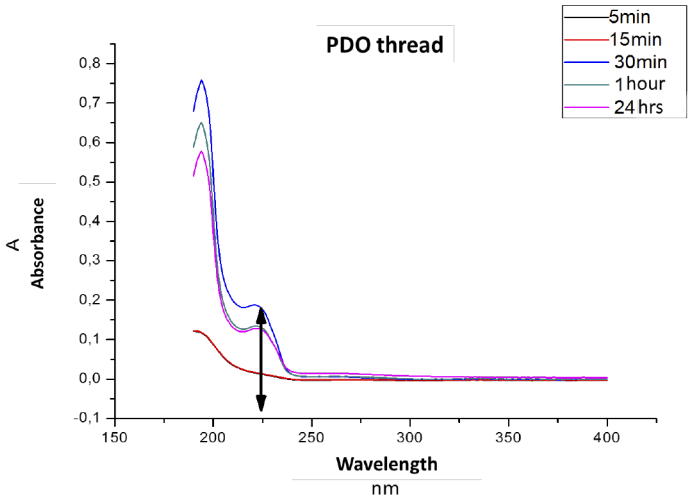
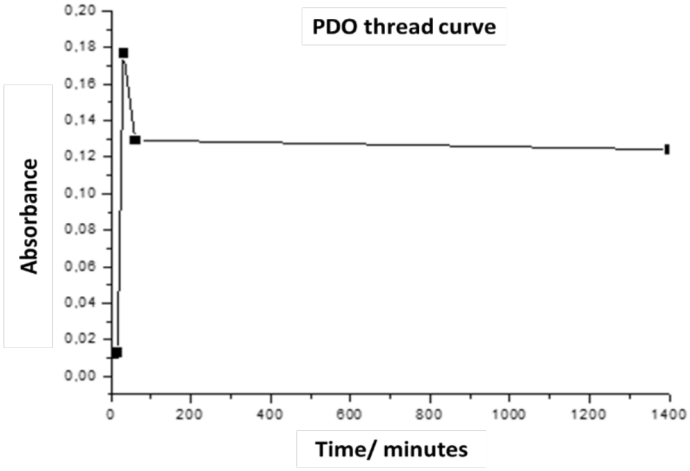


Figure 5. A. Topography of the PDO thread without the drug (control) SEM photomicrograph at 25X. Spicular fissures are observed at the lateral edges B. PDO thread with Arg. SEM photomicrograph at 150X. Note a layer that covers the thread, which interpenetrates the fissure of the fiber and that in certain sections it flakes. It corresponds to the asset fixed on the surface of the PDO thread.

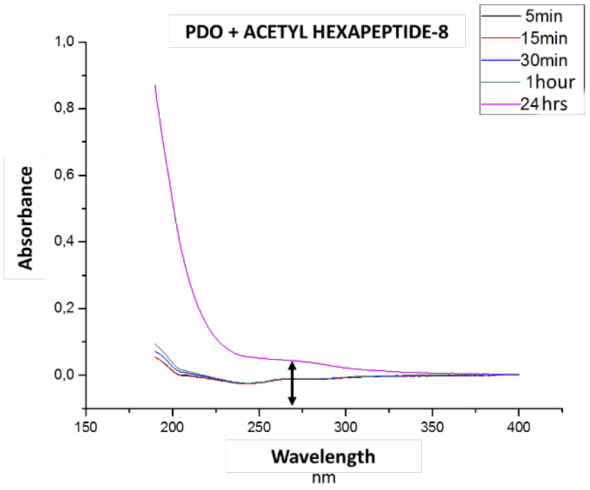


Graph 1. Absorbance spectrum of PDO suture.



Time	Absorbance signals of the PDO thread
5min	0.01211
15 min	0.01314
30 min	0.17686
60 min	0.1294
24 hrs	0.1242

Graph 2. Absorbance vs time curve for PDO.



Graph 3. UV-Vis spectrum of PDO at the time intervals in which the release of Arg was measured.

peak observed corresponds to the amorphous substance of the polymer that begins to be released into the medium by an incipient hydrolysis process that fails to destabilize and dissolve the structure.

Acetyl Hexapeptide Release from Polydioxanone Suture

Once the Arg is incorporated into the PDO, the release in distilled water is measured by UV-vis spectroscopy, Graph 3 evidence the UV-Visible spectrum of release as a function of time.

It can be seen that the absorbance area of the system is at a wavelength of approximately 270nm. Regarding the signals captured over time, it can be seen that at 15 minutes (red line) a signal was recorded in the middle that remained very close until 60 minutes (green). At 24 hours (pink), the highest absorbance peak was generated, among the registered signals, this could correspond to an abrupt exit, or the drug entering the medium, either due to the degradation of the scaffold that would cause the strands of the thread to break releasing the peptide in the middle, this being the strong signal captured by the equipment.

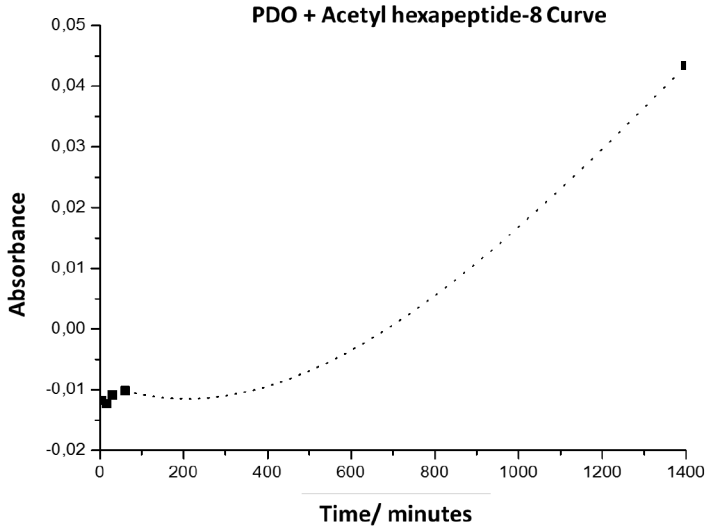
Estimation of the release kinetics of Acetyl Hexapeptide from Polydioxanone

The estimate of the release kinetics was calculated by plotting the absorbance as a function of time. Table 3 shows the results of the highest wavelength or highest peak absorbance of the PDO suture fragment with Arg studied at 5, 30, 60 minutes, and 24 hours, data taken for the graphic representation of the release curves corresponding to each scaffold.

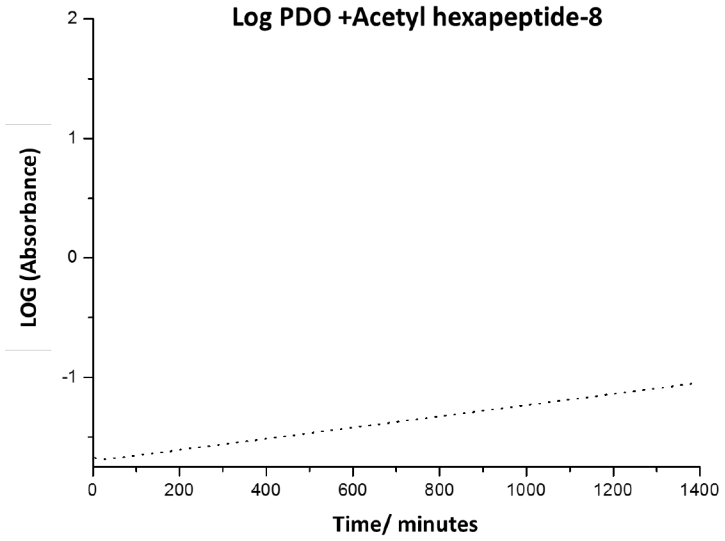
As it was not certain whether the spectrophotometer detected the DMAE signal from the scaffold (peak observed in graph 3), it was decided to determine the order of release kinetics, for which the absorbance was plotted as a function of time (Graphs 4 and 5).

Table 3. Drug absorbance from PDO as a function of time.

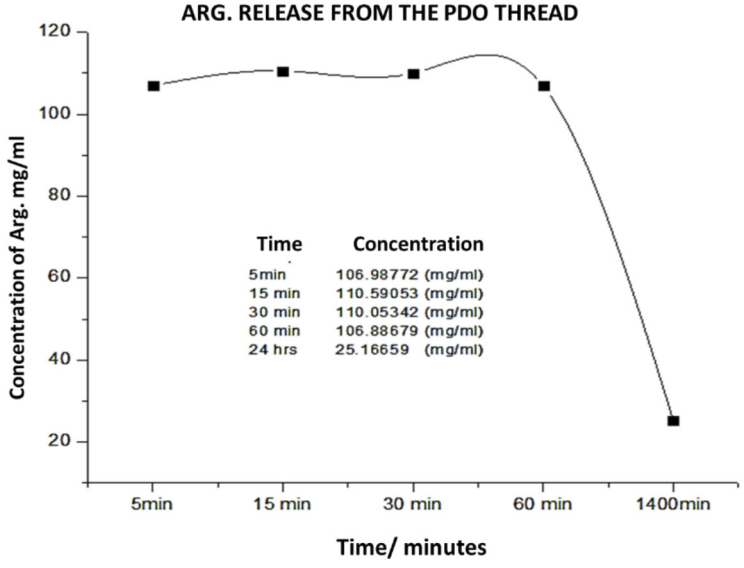
Time	PDO + Arg
5min	-0.01175
15 min	-0.01228
30 min	-0.01082
60 min	-0.01015
24 hrs	0.04341



Graph 4. Arg release curve from the PDO thread, representing the absorbance as a function of time.



Graph 5. Kinetics of release of Arg from the PDO thread, representing the absorbance as a function of time.



Graph 6. Arg concentration released over time from the PDO thread.

Graph 4 shows a slope in the form of a curve, indicating that the release of Arg from the PDO occurs at a starting point which is higher than zero. This indicates that it is a first-order reaction, in which the speed depends on the concentration of a reagent raised to the first power, meaning that it will depend on the concentration of species released into the environment; a graph of the Logarithm of absorbance as a function of time must be made to confirm the release kinetics (Graph 5).

Graph 5 reveals that at short times, the release kinetics obeys a straight line, which indicates that this system follows the first-order release, that is, it depends on the concentration of a substance in the system, kinetics that can be expressed according to Eq. 1

$$LnQ_t = LnQ_0 - K_0 t \quad \textbf{Eq. 1}$$

Where Qt is the amount of substance released at

time t, Q0 is the initial amount of drug in the solution, which is generally zero, and K0 is the constant rate in first-order kinetics.

APPEARING the shape of the slope indicates that the PDO thread

- is a good controlled release system for this drug
- would allow a sustained and slow release of said drug

PDO + Arg.

Released concentration vs time

To determine the amount or concentration released, the absorbance of the drug was converted to milligrams/milliliters, using the conversion factor (CF) formula according to the Lambert-Beer law, since absorbance is directly proportional to the concentration, recording the concentration for each of the absorbance recording periods studied (5, 15, 30, 60 minutes and 24 hours).

The release rate represented in graph 6, demonstrated that the peptide concentration in the medium was released in similar concentrations from 5 minutes to 60 minutes, when the curve falls to its minimum concentration until 24 hours, probably due to the exhaustion of the drug and saturation of the medium.

Discussion

Acetyl Hexapeptide-8 (Argireline®, Arg) is a hexapeptide, that is, a chain of six synthetically linked amino acids that has been positioned as a novel biomimetic active for the effect of botulinum toxin[9]. Its anti-wrinkle efficacy is the result of a double-action: on the one hand, it causes muscle relaxation through a mechanism like that of botulinum toxin; on the other hand, it causes the relaxation of fibroblasts and a lifting effect.

This inhibitory peptide of presynaptic neuronal exocytosis is used in anti-wrinkle formulations since the peptide in the active ingredient inhibits the contraction of the mimic muscles, especially the frontal ones, the cutaneous ones on the neck, those in the nasal area, and orbicularis of the eyelids[10]. It is made up of chains of six acetylated amino acids at the N-terminal residue; it is a weight molecule of 875 Da[11, 12].

The N-terminal end of acetyl hexapeptide-8 associates with the synaptosomal receptor for the synaptic protein SNAP25 in the SNARE complex, essential for neuronal exocytosis. This complex is destabilized, preventing the fusion of the catecholamine and acetylcholine vesicles with the membrane, blocking the release of Ca2, it is dependent on neurotransmitters (acetylcholine) at the neuromuscular junction, which mimics the activity of botulinum neurotoxin (BoNT) type A but without destroying the SNARE complex [12,13].

The effectiveness of acetyl hexapeptide-8 in preventing the formation of skin rhytids or its skin antiaging effect has been confirmed in several in vitro and in vivo tests in healthy volunteers[12]. Despite its excellent mimesis with BoNT A, transdermal penetration of acetyl hexapeptide-8 is limited due to its large molecular weight[14].

Apart from modifying the formulation, various techniques have been proposed for permeation through the stratum corneum, for example, chemical enhancers, iontophoresis[15], microneedles[16-19], son phoresis[20], thermal ablation[21], radiofrequency ablation[22], jet injectors[23] and electroporation[24, 25]. While these methods of skin permeation or skin penetration enhancers work for entry, a major obstacle for transdermal delivery remains their high molecular weight.

With a high molecular weight of 889 Dalton, Arg remains primarily on the surface of the skin after a topical application 0.01% of the peptide reaches the epidermis without traces of the peptide in the dermis. Poor skin permeation can lead to a significant peptide waste, resulting in an ineffective final dosage form[26].

It is because of this limited transdermal permeation that we propose to load the PDO suture as an intradermal delivery system for the acetyl hexapeptide, used successfully in the neuromodulation of the frontal and periocular areas under a new protocol of bioactive sutures for Facial Harmonization.

The PDO threads analyzed in this investigation emit the highest signal of Arg release at 24 hours, and are not studied for a longer period because it was considered that from these results, projections of the release curve could be made. The plateau shape is maintained for 1 hour, which indicates that in these

60 minutes the release of almost all the content of the peptide from the PDO occurs, but is carried out in a sustained and controlled manner. This indicates that it is a favorable release profile for the supply of the active ingredients and its progressive and selective action on the Snare complex, concentrating in 1 hour what would probably be achieved topically by intradermotherapy after 4 weeks[15].

However, evidence found in the literature indicates that when using PDO threads as release matrices there is a spike in the release after approximately 30-40 days, caused by mechanisms of controlled degradation in longer times[27], which could result in such.

In addition, the absorbance region observed versus the time graphs for the PDO + Arg system between 200 to 270nm is similar to the range determined by other authors for Arg alone, which has its maximum peak at 215 nm when acetyl analyzed hexapeptide through UV-Vis[28] spectroscopy. This similarity between our results and those of these authors suggests that indeed, what was captured by the spectrophotometer in the aqueous medium corresponds to Arg being released into the medium, and not traces of PDO suture.

This seems to be the result of the combination of a diffusion and a degradation effect, so that PDO threads made of nanofibers are resistant to fluid absorption once inside the body and, therefore, produce a much smaller diffusion of the solute outside the polymer and therefore more controlled[27].

The hydrolytic degradation of PDO suture is partially affected by the degree of crystallinity of the compound but can be accelerated by the action of the impregnated substance. In general, the swelling of the PDO suture and its subsequent degradation begins in the amorphous regions and spreads towards the crystalline regions[7, 29], as observed in the optical photomicrographs of the present study. However, the electronic microphotographs confirm that despite the swelling of the PDO thread due to its capillarity, the topography of the Arg-embedded thread remains without any physical degradation in the short periods evaluated.

Likewise, the peptide release graphs from the PDO suture reveal that the thread constitutes an ideal system for the sustained release of acetyl hexapeptide-8, this being a kinetic similar to that observed in the most versatile polymer devices currently used for other purposes. However, clinical trials must be carried out to determine the efficacy of PDO thread as an Acetyl Hexapeptide-8 delivery system, which is expected to generate a lifting superior to its intradermal injection. Its clinical results should also be compared with its gold standard counterpart, botulinum toxin type A.

Nonetheless, no signs of cytotoxicity have been observed in human dermal fibroblasts and human epidermal keratinocytes, when Arg is administered in concentrations between 10 μg / ml and 1 mg/ml, if there is an anti-cell proliferation effect with Arg at 48 h of incubation in cell cultures with doses of 100 μM (90 μg / ml). Therefore, the use of acetyl hexapeptide-8 (Argireline®) in very high doses or for a very long period should be considered potentially dangerous[30]. Consequently, it suggested attending to this dosage when applying directly intradermally using polydioxanone threads impregnated with acetyl hexapeptide.

Conclusions

- The instrumental analysis of the polydioxanone suture under four types of analytical techniques, evidenced for the first time in the scientific literature, the capacity of the PDO suture as an intelligent system for the controlled release of acetyl hexapeptide-8.
- The fluid absorption test completed through electronic weighing revealed that the PDO thread has capillarity, as it doubles its weight every 24 hours until 72 hours of evaluation when soaked with acetyl hexapeptide-8.
- Controlled release tests show that PDO threads are a good osmotically controlled release system for acetyl hexapeptide-8, allowing a slow and sustained release of it from 5 minutes to 24 hours.
- In a period of 60 minutes, the biomimetic peptide is released almost completely, but in a sustained and controlled way (plateau shape), so this release profile is favorable for the subdermal supply of the action since its action on the complex Snare concentrates in 1 hour what would be achieved progressively topically through intra-dermotherapy after four weeks.

- Both, the optical photomicrographs and the electronic photomicrographs confirm that despite the swelling experienced by the PDO thread due to its capillarity, the topography of the thread that is embedded with acetyl hexapeptide remains without physical degradation in the evaluated lapses.
- Capillarity can be an ally in Facial Harmonization if PDO sutures are used as a controlled release system, turning PDO sutures into bioactive scaffolds, capable of releasing Arg while maintaining its resistance modulus without prematurely degrading.
- It suggested carrying out clinical trials to determine the anti-wrinkle efficacy of the polydioxanone thread loaded with acetyl hexapeptide-8, to demonstrate that this system and novel proposal will generate a lifting superior to its intradermal injection. Its clinical results should also be compared with its gold standard counterpart, botulinum toxin type A.

Roles authoring: VGG: conceptualisation, methodology, formal analysis, research,resourses, writing - original project preparation, writing - revision and edition, visualization, supervision, project management. DSV: conceptualisation, methodology, formal analysis, research, resources, writing - original project preparation, writing - revision and editing, displaying, supervision, project management. GVM: conceptualisation, methodology, formal analysis, research, resources, writing - original project preparation, writing - revision and editing, visualization, supervision, project management. ROR: conceptualisation, methodology, formal analysis, research, resources, writing - original project preparation, writing - revision and editing, visualization, supervision, project administration. BMK: conceptualisation, methodology, formal analysis, research, resources, writing - original project preparation, writing - revision and editing, visualization, supervision, project management.

Acknowledgment: To the Laboratory of Electrochemistry at the Faculty of Science at the University of the Andes, Venezuela for facilitating access to the laboratory facilities and for carrying out the in vitro degradation test and monitoring their implementation. Thanks to "Dr Ernesto Palacios Pru" Scanning electron microscopy Center at the Medicine Faculty of the University of the Andes, Venezuela for the help in the processing of samples, guidance in the microscopical observation and recording visual proof.

Declaration of conflicts of interest: The authors completed the declaration of conflict of interests of ICMJE and declare that they have not received funds to complete the report; they have no financial relationships with organizations that may be interested in an article published in the last three years; and have no other relationships or activities that could influence the published article. The forms can be requested by contacting the responsible author or the editorial board of the Journal.

Financing statement: The authors stated that there were no external funding sources.

References

1. Zamani F, Jahanmard F, Ghasemkhah, et al. Nanofibrous and nanoparticle materials as drug-delivery systems. In Nanostructures for Drug Delivery; Elsevier Inc.: Amsterdam, The Netherlands, 2017; pp. 239–270.
2. Yu DG, Li JJ, Williams GR, Zhao M. Electrospun amorphous solid dispersions of poorly water-soluble drugs: A review. J Control Release. 2018; 292:91-110.
3. Suárez-Vega DV, Velazco de Maldonado GJ, Ortíz RL, García-Guevara VJ, Miller-Kobisher B. In Vitro Degradation of Polydioxanone Lifting Threads in Hyaluronic Acid. J Cutan Aesthet Surg. 2019; 12(2):145-148.
4. Padmakumar S, Joseph J, Neppalli MH, et al. Electrospun Polymeric Core-sheath Yarns as Drug Eluting Surgical Sutures. ACS Appl Mater Interfaces. 2016; 8(11):6925-34.
5. Joseph J, Krishnan AG, Cherian AM, et al. Transforming Nanofibers into Woven Nanotextiles for Vascular Application. ACS Appl Mater Interfaces. 2018; 10(23):19449-19458.
6. Gladys Vidarte. Suturas. Dermatol Per [Internet]. 2001; 11 (Suppl 1):7-12. Available from: https://sisbib.unmsm.edu.pe/bvrevistas/dermatologia/v11_sup1/suturas.htm
7. Medeiros AM, Araújo-Filho I, Carvalho MDF. Fios de sutura. J Surg Cl Res [Internet]. 2016; 7(2):74-86. Available from: https://periodicos.ufrn.br/jscr/article/view/11437
8. Hurtado J. Metodología de la Investigación. Guía para la comprensión holística de la ciencia. Quirón Ediciones. 4ta ed. 2010. Caracas-Venezuela. Available from: https://dariososafoula.files.wordpress.com/2017/01/hurtado-de-barrera-metodologicc81a-de-la-investigaciocc81n-guicc81a-para-la-comprensiocc81n-holicc81stica-de-la-ciencia.pdf
9. M Teresa Alcalde. Productos cosméticos con efecto Botox. Offarm vol. 23issue 7(2004)pp: 92-99 Published by Elsevier. Available from: https://www.elsevier.es/en-revista-offarm-4-articulo-productos-cosmeticos-con-efecto-botox-13064297
10. Gorouhi F, Maibach HI. Role of topical peptides in preventing or treating aged skin. Int J Cosmet Sci. 2009; 31(5):327-45.
11. Ruiz MA, Clares B, Morales ME, Cazalla S, Gallardo V. Preparation and stability of cosmetic formulations with an anti-aging peptide. J Cosmet Sci. 2007; 58(2):157–171.
12. Blanes-Mira C, Clemente J, Jodas G, et al. A synthetic hexapeptide (Argireline) with antiwrinkle activity. Int J

Cosmet Sci. 2002; 24(5):303-10.
13. Blanes-Mira C, Merino JM, Valera E, et al. Small peptides patterned after the N-terminus domain of SNAP25 inhibit SNARE complex assembly and regulated exocytosis. J Neurochem. 2004; 88(1):124-35.
14. Kraeling ME, Zhou W, Wang P, Ogunsola OA. In vitro skin penetration of acetyl hexapeptide-8 from a cosmetic formulation. Cutan Ocul Toxicol. 2015; 34(1):46-52.
15. Krishnan G, Roberts MS Grice, J Anissimov, YG Moghimi, HR Benson, HAE (2014). Permeación cutánea iontoforética de péptidos: una investigación sobre la influencia de las propiedades moleculares, las condiciones iontoforéticas y los parámetros de formulación. Drug Deliv Transl Res. 4, 222–232.
16. Ling MH, Chen MC. Disolver parches de microagujas de polímero para una administración transdérmica rápida y eficiente de insulina a ratas diabéticas. Acta biomaterialia. 2013; 9: 8952–8961.
17. Katsumi H, Quan YS, Kamiyama F, Kusamori K, Sakane T, Yamamoto A. [Development of a novel transdermal delivery system of peptide and protein drugs using microneedle arrays]. Yakugaku Zasshi. 2014; 134(1):63-7.
18. Liu S, Jin MN, Quan YS, et al. The development and characteristics of novel microneedle arrays fabricated from hyaluronic acid, and their application in the transdermal delivery of insulin. J Control Release. 2012; 161(3):933-41.
19. Mohammed YH, Yamada M, Lin LL, et al. Microneedle enhanced delivery of cosmeceutically relevant peptides in human skin. PLoS One. 2014; 9(7):e101956.
20. Luis J, Park EJ, Meyer RJ, Smith NB. Rectangular cymbal arrays for improved ultrasonic transdermal insulin delivery. J Acoust Soc Am. 2007; 122(4):2022–2030.
21. Banga AK. Microporation applications for enhancing drug delivery. Expert Opin Drug Deliv. 2009; 6(4):343–354.
22. Levin G, Gershonowitz A, Sacks H, et al. Transdermal delivery of human growth hormone through RF-microchannels. Pharm Res. 2005; 22(4):550-5.
23. Mitragotri S. Current status and future prospects of needle-free liquid jet injectors. Nat Rev Drug Discov. 2006; 5(7):543-8.
24. Kalluri H, Banga AK. Transdermal delivery of proteins. AAPS PharmSciTech. 2011; 12(1):431-41.
25. Zhao YL, Murthy SN, Manjili MH, Guan LJ, Sen A, Hui SW. Induction of cytotoxic T-lymphocytes by electroporation-enhanced needle-free skin immunization. Vaccine. 2006; 24(9):1282-90.
26. Lim SH, Sun Y, Thiruvallur Madanagopal T, Rosa V, Kang L. Enhanced Skin Permeation of Anti-wrinkle Peptides via Molecular Modification. Sci Rep. 2018; 8(1):1596.
27. Smrithi Padmakumar, Bindhu Paul-Prasanth, K Pavithran, et al. Long-term drug delivery using implantable electrospun woven polymeric nanotextiles. Nanomedicine. 2019; 15(1):274-284.
28. Makowska J, Tesmar AM, Wyrzykowski D, Chmurzynski L. Investigation of the Binding Properties of the Cosmetic Peptide Argireline and Its Derivatives Towards Copper(II) Ions. J Solution Chem. 2018; 47:80–91.
29. Sabino M, Márquez L y Feijoo J. Estudio de la degradación hidrolítica de la polidioxanona para la predicción del tiempo de vida útil. Rev Tec Ing Univ Zulia. 1998; 21(3):170-178.
30. Grosicki M, Latacz G, Szopa A, Cukier A, Kieć-Kononowicz K. The study of cellular cytotoxicity of argireline - an anti-aging peptide. Acta Biochim Pol. 2014; 61(1):29-32.

Received:29 January 2022
Accepted: 21 June 2023

Corresponding author:
Garcìa-Guevara Vìctor.
Fundaciòn Centro de Estudios de Medicina Estètica (FUCEME), Maracay Street, Quinta Riva, El Marques Urbanization, Horizonte Sector, Caracas - Venezuela.
Phone: +58 212 2375798
E-mail: fuceme@gmail.com